UNDATED

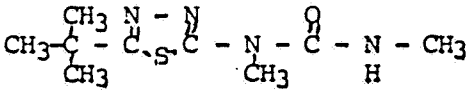
FAP-5H5066/TXR-543

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

000347

SUBJECT: PP# 5G1562/FAP# 5H5066: Tebuthiuron (EL-103) in sugarcane at 0.1 ppm (negligible residues) and in sugarcane molasses, syrup and bagasse at 0.3 ppm; proposal for temporary tolerances.

DATE: FEB 21 1975



FROM: TB

TO: Product Manager Herbicides/Fungicides Br.

Petitioner: Elanco Products Co.

Indianapolis, Indiana

Related Petitions: None - new chemical

TOXICOLOGICAL REVIEW

1. Acute Toxicity

Toxicity data submitted in support of a non-agricultural registration (1471-EXP) were reviewed by B. Jaeger, 11/7/74 and are here summarized:

Acute Oral

Technical, Mouse	(M)	LD50 542-579 mg/kg
	(F)	LD50 528-620 mg/kg
Technical, Rat	(M)	LD50 720 mg/kg
	(F)	LD50 596-626 mg/kg
Technical, Rabbit		LD50 286 mg/kg
Technical, Cat		LD_{50} >200 mg/kg (largest dose tested)
Technical, Dog		LD50 >500 mg/kg (largest dose tested)
Technical, Chicken		LD50 >500 mg/kg (largest dose tested)
80 WP, Rat	(F)	LD50 632 mg/kg
	(M)	LD_{50} 900 mg/kg

Recommendation:

PP# 5G1562: - Sugarcane at 0.1 ppm (negligible residues) tebuthiuron.

Toxicity data in registration jacket #1471-97 Spike 80W by reference to this petition support the proposed temporary tolerance of 0.1 ppm (negligible residues) tebuthiuron per se in sugarcane. We therefore recommend that it be established. CB have concluded that there may be a problem with metabolites but that this level is adequate for the parent compound per se (review of A. Smith, 1/31/75).

FAP# 5H5066: - 0.3 ppm in sugarcane molasses, syrup and bagasse.

There are insufficient toxicity data to permit this non-negligible residue level in these food items. CB have also concluded that there are insufficient residue data as to the potential metabolites. We cannot therefore draw any conclusions as to the safety of the proposed tolerances until CB can make an estimate as to how much of a tolerance is needed.

Petitioner should be informed at this time that he will need long-term studies in order to support non-negligible residue tolerances.

Dermal Toxicity

Technical, Rabbit	LD_{50} >200 mg/kg (largest dose tested)
80 WP, Rabbit	LD_{50} >500 mg/kg (largest dose tested)

Inhalation Toxicity

80 WP, Rat	LD_{50} >8.56 mg/l of air (largest dose tested—rats had chromorhinorrhea and chromodacryorrhea while in chamber)

Eye Irritation

Technical, Rabbit	No irritation noted in corneal membranes or in folds of the iris.
80 WP, Rabbit	Irritation continued to palpebral conjuctival membrane with slight hyperemia, chemosis, and discharge.

2. Subacute Toxicity Data

(Submitted in support of registration # 1471-97, Spike *80W).

A. 3 Month rat Feeding Study (#R-491)

Methods:

Harlan rats (28 - 35 Gm) were randomized into four groups of 10 male and 10 females each and were offered diets containing 0, 400, 1000 or 2500 ppm EL-103 for three months. Animals were monitored for appearance, behavior, food intake, body weights, food efficiency utilization and mortality. Eye were examined initially and at termination. Blood samples were obtained terminally and Hct., Hb., RBC's, total and differential leukocytes, prothrombin times; BUN, Glucose, SGPT were determined.

Histopathological examination was performed on the following tissues and organs: (*) weights obtained

liver*	heart*
kidney*	spleen*
thyroid*	adrenals*
gonads*	prostate*
uterus*	large gut
small gut	lungs
lymph node	mammary gl.
pancreas	salivary gl.
stomach	muscle
thymus	urinary bladder

Results:

High dose males and females demonstrated decreased body weights; increased liver, kidney and gonad weight ratios; males showed in addition increased ratios for spleen and prostate gland. There was a suggestion of thyroid hypertrophy in the middle dose males and females, but not in the high dose-animals.

Clinical chemistry findings were not altered at any level by treatment.

Adverse histopathological findings were confined to the appearance of a vacuolization of the acinar cells of the pancreas at the 2500 ppm level.

Conclusions:

The 90 day rat feeding NEL is 1000 ppm EL-103 based on systemic effects of altered organ/body weight ratios and the appearance of adverse histopathology of the pancreas in high dose animals.

B: Dog 90 day feeding study (D-398-71)

Methods:

Pure-bred Beagle dogs were divided into four groups of two females and two males each and were offered diets containing 0, 500, 1000 or 2500 ppm EL-103 for 3 months (90 days). The animals were observed for appearance, behavior, food consumption and body weight initially and at suitable intervals thereafter. Ophthalmoscopic examination of the eyes was done initially and a termination. Blood samples were obtained initially and at 1, 2 and 4 weeks and at monthly intervals thereafter. These were examined for calcium, inorganic phosphorus, glucose, BUN, Cholesterol, total protein, albumin, total bilirubin, Alk. Ph., LDH, and SGOT. In addition, Hb., Gct., REC's total and differential leukocytes, reticulocytes, clotting time, platelets, sed rate and prothrombin times were determined.

Gross and microscopic histopathology was performed and the following organs and tissues were examined: (*)= weights obtained.

liver*	kidney*
heart*	spleen*
gonads*	adrenals*
thyroid*	brain
marrow	large and small gut
gall bladder	lungs
lymph nodes	mammary gl.
pancreas	putuitary
salivary gl.	stomach
muscle	thymus
bladder	prostate/uterus

Urine samples were obtained and examined for sugar, pH, protein, blood and Sp. Gr.

Results:

Anorexia was noted especially in the high-dose animals, leading to some weight loss. There was no mortality. Behavior, and appearance were unremarkable at all test levels. No abnormalities were seen in the hematological or urinalyses studies.

Clinical chemistry findings indicated increased BUN in the 2000 ppm females; in addition, this group exhibited increasing levels for Alkaline phosphatase, up to four-fold over that of controls. Levels of this parameter had returned to normal at the terminal sampling. The 2000 ppm males likewise demonstrated this finding. There were no urinary abnormalities.

1000 ppm females and males demonstrated increased thyroid/body weight ratios and the 2000 ppm females also showed increased spleen ratio.

Histopathological findings were negative for adverse effect of EL-103.

Conclusions:

The systemic NEL for feeding of EL-103 to dogs for three months is considered to be 500 ppm on the basis of increased thyroid ratios, increased Alkaline phosphatase values and increased BUN in test animals.

C. Rat Teratology Study (R-632)

Methods:

Pregnant Harlen rats were offered diets containing 0, 600, 1200 or 1800 ppm EL-103 during gestation days 6-15. Pups were obtained by Ceasarian section and were examined for weight, sex distribution, external visceral and skeletal anomalies. Uteri and ovaries were examined for corpora lutea, distribution of fetuses, resorptions and litter size.

Approximately a third of the fetuses in each litter were fixed in buoin's solution for visceral examination and the remainder were cleared for skeletal examination.

Results:

Abnormalities of somatic architechture were few in number and low in severity and were not dose related. Body weights and other paramaters were not adversely affected.

Conclusions:

EL-103 is not a teratogen in rats at up to 1800 ppm when given in the diet during days 6-15 of gestation.

D. Metabolism of EL-103

1. Single oral dose in rats dogs and rabbits - labeled material: excreted in the urine almost exclusively and virtually all within 72 hours.

2. Urinary metabolites were identified (Table I) and their distribution in the rat, dog and rabbit urine was determined (Table II).

David L. Ritter 2/21/75
Toxicology Branch
Registration Division

cc: CB, EFEB, Branch File

R/D Init: G.E. Whitmore 2/21/75

Init: G.E. Whitmore

DLRitter:gac 2/21/75

TABLE I

METABOLISM of EL-103

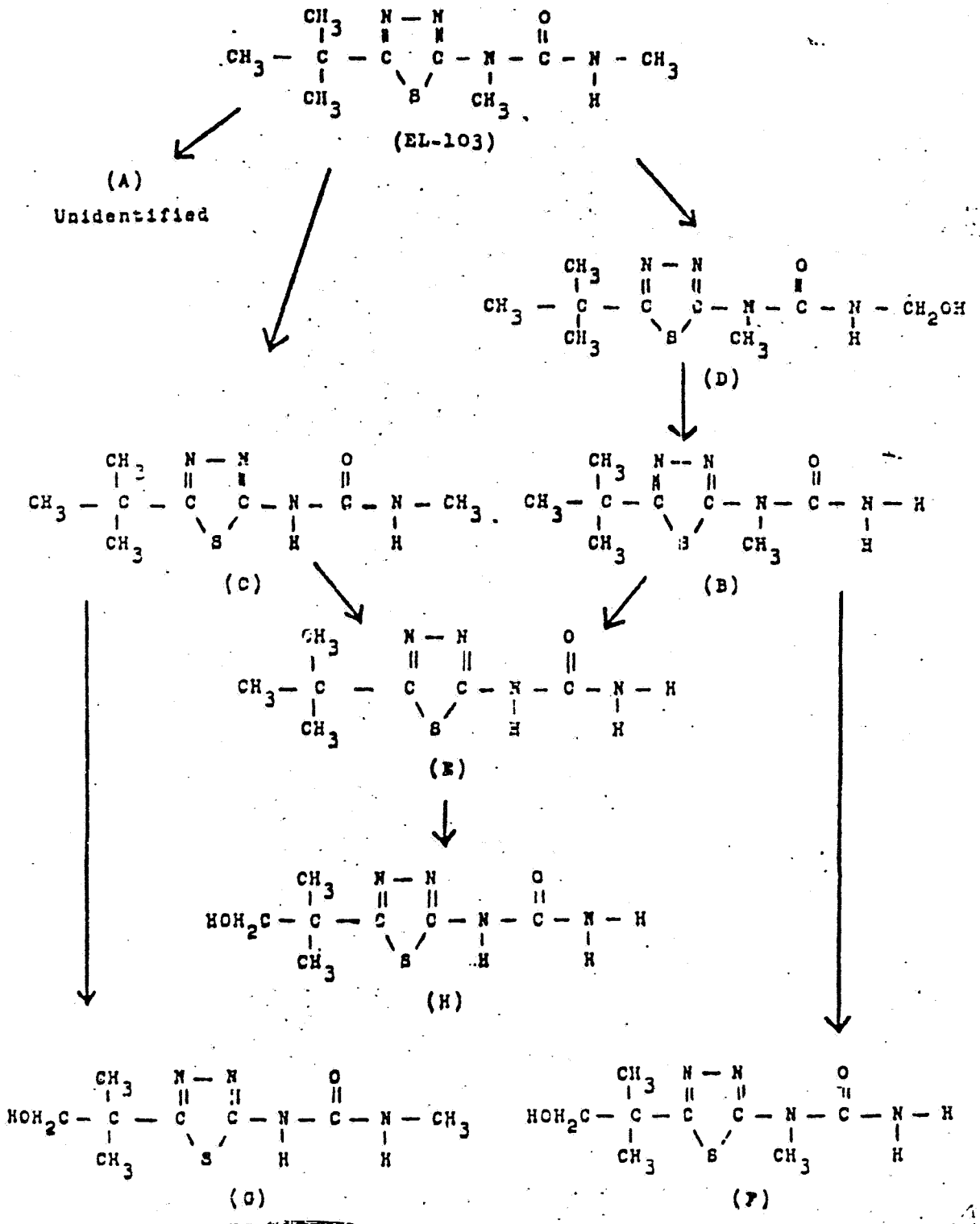


TABLE 11

SPECIES DIFFERENCES IN THE EXCRETION OF URINARY METABOLITES FOLLOWING AN ORAL DOSE OF ^{14}C-103 (10 MG/KG)

COMPOUND EXCRETED	RADIOACTIVITY (% IN URINE EXTRACT)*			
	RAT	RABBIT	DOG	ICK
103	0.7	0.4	0.6	
METABOLITE A	0.2	0.1	2.9	
B	10.9	15.2	4.9	
C	6.1	28.8	15.0	
D	11.8	0.2	3.2	
E	15.0	22.8	40.2	
F	36.7	20.4	14.4	
G	8.5	6.8	9.2	
H	10.1	5.3	9.6	

* The radioactivity at the R_f value of the metabolite is expressed as a percentage of the total radioactivity on the plate.